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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/412,297	10/05/1999	KANG TING	3100.006US0	9486

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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/412,297	TING, KANG
	Examiner	Art Unit
	Vanessa L. Ford	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2002*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed March 26, 2002. Claims 1 and 2 have been amended. Claims 3-7 and 13-49 have been cancelled.

2. Applicant's submission of a computer readable form (CRF), a paper copy of the sequence and a statement stating that the paper copy and CRF are the same are acknowledged.

3. The Applicant's Declaration filed on March 26, 2002 under 37 CFR 1.131 has been considered but is ineffective to overcome the Ting et al reference. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Ting et al reference. The Declaration is ineffective because it recites "Exhibit A" which is not attached to the Declaration. Therefore, there are no data to establish reduction to practice prior to the date of the of the Ting et al Reference.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections and Rejections Withdrawn

5. a) Objection to the specification, page 4, paragraph 3, of previous Office action.
b) Objections to the drawing, page 4, paragraph 4, of the previous Office action.
c) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, page 4, paragraph 5 of previous Office action.
d) Rejection of claim 1 under 35 U.S.C. 112, second paragraph, pages 4-5, paragraph 6 of previous Office action.
e) Rejection of claims 1-2 under 35 U.S.C. 112, second paragraph, page 5, paragraph 7 of previous Office action.
f) Rejection of claim 2 under 35 U.S.C. 112, second paragraph, page 5, paragraph 8 of previous Office action.

Objections and Rejections Maintained

6. The rejection of claims 1 and 8-12 under U.S.C. 102(b) as being anticipated by Kuberasampath et al in view of Ting et al and further in view of Siris et al is maintained for the reasons set forth in paper 8, paragraph 9 of the previous Office action.

The rejection was on the grounds that Kuberasampath et al teach a method of screening for candidate compounds with alter bone mass or preventing bone loss (i.e. bone mineralization). Kuberasampath et al teach candidate compounds that may alter the expression of morphogens by incubating the cell in culture with the compound in order to assess the effects of the compound on the cell. Kuberasampath et al that this can be accomplished by detection of the morphogen either at the protein or RNA level (columns 36-38).

Kuberasampath et al do not specifically teach assay methods for testing compounds which effect the expression of the Nell-1 gene.

Ting et al teach human Nell-1 expressed in Unliteral Coronal Synostosis (UCS) Ting et al teach a method of screening by demonstrating that DD-PCR can be applied to identify genes up or down-regulated in Unliteral Coronal Synostosis. The DD-PCR screening process was used to detect the Nell-1 PCR product in a normal cranial suture and an abnormal cranial suture on four UCS patients. Ting et al teach that the PCR products were analyzed on a 1% agarose gel and confirmed by Southern blotting using the labeled cDNA clone as a probe (page 82). Ting et al teach the identification of cells

expressing Nell-1 within the suture site using *in situ* hybridization. Ting et al teach that human multi-organ tissue mRNA blot showed that the Nell-1 was expressed in rat calvarial osteoprogenitor cells and was largely absent in rat tibiae and fibroblast cell cultures. Ting et al teach that Nell-1 and it related molecules may represent a new class of proteins involved in growth and development. Ting et al demonstrated the increased expressions of Nell-1 in intramembranous bone formation and in the pathological entity of premature UCS (page 88).

It would be *prima facie* obvious to one skilled in the art at the time the invention was made to test for compounds that effect the expression of the Nell-1 gene by contacting a cell containing the Nell-1 gene with a test agent because Kuberasampath et al teaches screening assays for candidate compounds which alter a gene which produces a protein that stimulates bone formation, i.e., bone mineralization. Since the Nell-1 gene, as taught by Ting et al, is also known to produce a protein that enhances bone mineralization it would have been obvious to one of ordinary skill in the art to screen for compounds which may positively effect expression of the gene and thereby increase bone mass and/or prevent bone loss.

The Applicant urges that Ting et al is not prior art to the instant application. Applicant urges that Kuberasampath et al alone do not render the inventions of claims 1 and 8-12 obvious. Applicant urges that Kuberasampath et al do not specifically teach assay methods for testing compounds which effect expression of the Nell-1 gene.

Applicant's arguments filed March 26, 2002 in paper No. 10 have been fully considered but are not persuasive. As stated previously (paragraph 3), Ting et al is considered as prior art in view of the ineffective Declaration under 37 CFR 1.131. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. Kuberasampath et al teach a method of screening for candidate compounds with alter bone mass or preventing bone loss (i.e. bone mineralization). Kuberasampath et al do not specifically teach assay methods for testing compounds which effect the

expression of the Nell-1 gene. Ting et al teach human Nell-1 expressed in Unliteral Coronal Synostosis (UCS). There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

7. The rejection of claim 2 under U.S.C. 103(a) as being unpatenable over Kuberasampath et al in view of Siris et al is maintained for the reasons set forth in paper 8, paragraph 10 of the previous Office action.

The rejection was on the grounds that Siris et al teach a database the that contains information on several hundred thousand subjects. Siris et al further teach that this database will contain peripheral and central measurements of bone density and relate these factors, treatment patterns and the natural history of osteoporosis.

It would be *prima facie* obvious to one skilled in the art at the time the invention was made to add the modulators of bone mineralization as taught by Kuberasampath et al in combination with Ting et al to the database of Siris et al because Siris et al teach that the database will provide a resource that is unmatched in size and scope in the medical field and will allow for future research in a number of areas including patient outcomes, types of follow-up employed in clinical practice, diagnostic cost modeling and osteoporosis therapy use (see Abstract).

Applicant urges that the combination of Kuberasampath et al and Siris et al fail to provide the elements of claim 2. Applicant urges that Kuberasampath et al do not specifically teach assay methods for testing compounds which effect expression of the Nell-1 gene. Applicant urges that the combination of Ting et al fails to provide a motivation to combine or reasonable expectation of success. Applicant urges that Ting et al do not teach that NELL-1 is a morphogen or has properties of morphogens as described by Kuberasampath et al. Applicant urges that one skilled in the art would not

recognize NELL-1 to be a morphogen and therefore there is no motivation to combine the teachings.

Applicant's arguments filed March 26, 2002 in paper No. 10 have been fully considered but are not persuasive. The applicant's arguments are not commensurate in scope with the claimed invention. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The applicant is also arguing limitations that are not in the claimed invention. There are no claim limitations that recite "morphogens". Claim 2 is drawn to the method of claim 1, further comprising recording test agents that alter expression of the Nell-1 nucleic acid or Nell-1 protein in a database of modulators of Nell-1 activity or in a database of modulators of bone mineralization. Kuberasampath et al teach a method of screening for candidate compounds which alter bone mass or prevent bone loss (i.e. bone mineralization). Kuberasampath et al do not specifically teach assay methods for testing compounds which effect the expression of the Nell-1 gene. Ting et al teach human Nell-1 expressed in Unliteral Coronal Synostosis (UCS). Kuberasampath et al and Ting et al as combined do not teach databases. Siris et al teach a database that contains information on several hundred thousand subjects. Siris et al further teach that this database will contain peripheral and central measurements of bone density and relate these factors to other risk factors, treatment patterns and the natural history of osteoporosis. Since the Nell-1 gene, as taught by Ting et al, is also known to produce

a protein that enhances bone mineralization it would have been obvious to one of ordinary skill in the art to screen for compounds which may positively effect expression of the gene and thereby increase bone mass and/or prevent bone loss and place these compounds in a database because Siris et al has shown the usefulness of maintaining this kind of information.

Applicant urges that the rejection is based on hindsight and is considered to be improper because Ting et al teaches that NELL-1 plays a role in enhancing bone mineralization and Ting et al does not teach that the NELL-1 gene produces a protein that enhances bone mineralization.

It is the Examiner's position that NELL-1 encodes a 421 amino acid (i.e. protein) from the carboxy-terminal end of the gene which is taught by Ting et al (page 86, 2nd column). Ting et al teach that the nel-1 related molecules are unknown. Ting et al also teach that nel-1 related molecules have a well conserved structure and the temporally and spatially localization expression patterns during development are suggestive of important roles during embryogenesis. Ting et al suggests that the nel-related molecules are associated with human developmental anomaly (page 87, 1st column). Ting et al further suggest that NELL-1 and its related molecules may represent a new class of proteins involved in growth and development (page 88, 1st column). Therefore, one of ordinary skill in the art could reasonably conclude that the protein encoded by NELL-1 enhances bone mineralization.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
June 12, 2002

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